Remarks

Prior to entry of this amendment, claims 1-20 were pending in the application. Claims 2 7, 15 and 18 are canceled herein. Claims 1, 3-6, 8, 10-14, 17 and 19-20 are amended herein. New claims 21-25 are added herein.

Claim 1 is amended to correct form and incorporate the limitations of claims 2 and 8. Additional support for the amendment of claim 1 can be found throughout the specification, for example on pages 10, 14 and 25. Claims 3-6 are amended to correct dependency. Claim 6 is amended herein to correct form. Claims 8 and 10 are amended to correct dependency, and remove a limitation now recited in claim 1. Support for the amendment to claim 11 can be found throughout the specification, for example on pages 3-5and 8-9. Claims 12-14, 17 and 19 are amended to correct dependency. Additional support for the amendments to claim 12 can be found throughout the specification, such as on page 8. Support for the amendment of claim 20, and for new claim 21, can be found in the specification at page 10, page 14, and in the original claims, such as claims 1, 3, 11, 15 and 17. Support for new claims 22-26 can be found throughout the specification, for example on pages 10, 11, 14 and 25.

Thus, after entry of this amendment, **claims 1, 3-6, 8-14, 16-17 and 19-26 are pending.** Reconsideration of the subject application is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly the use of IL-2 receptor antagonists are not enabled by the specification. Applicants respectfully disagree with this assertion. However, solely to advance prosecution, the claims have been amended to be limited to the use of antibodies that specifically bind the IL-2 receptor. Applicants reserve the right to prosecute any deleted subject matter in a continuation application.

The Office action confirms that the use of anti-Tac (p55) antibodies, such as daclizumab, basiliximab, BT563 and 7G8 are fully enabled by the specification. Applicants submit that the specification is also fully enabling for antibodies that specifically bind p75 (also known as beta). The specification fully describes antibodies that bind the IL-2 receptor (see for example, page 8, 3rd paragraph to page 9). The specification discloses that antibodies of use can bind the beta

chain of the IL-2 receptor. The specification discloses that Mig beta-2 is an exemplary antibody of use that binds p75.

Given the guidance provided by the specification, one of skill in the art could readily identify an antibody that specifically binds p75 that is of use in the presently claimed methods. For example, one of skill in the art could readily identify U.S. Patent No. 5,530,101 (Queen et al.) as disclosing antibodies that bind p75 that are of use in the presently claimed methods.

In view of the amendment of the claims, and these remarks, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly the treatment of any autoimmune disease is not enabled by the specification. Applicants respectfully disagree with this assertion. However, solely to expedite prosecution, the claims have been amended to be directed to methods for treating multiple sclerosis. Applicants reserve the right to prosecute any unclaimed subject matter in a continuation application.

Claims 1-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly there is insufficient written description for an IL-2 receptor antagonist other than anti-Tac antibodies. Applicants respectfully disagree with this rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, for example, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116, and MPEP § 2163.

The specification fully describes antibodies that bind the IL-2 receptor (see for example, page 8, 3rd paragraph to page 9). The specification discloses that antibodies of use can bind the beta chain of the IL-2 receptor. The specification discloses that Mig beta-2 is an exemplary antibody of use that binds p75.

Applicants submit that antibodies that bind the IL-2 receptor, including p75 are well known to one of skill in the art. Antibodies that bind p75 of the IL-2 receptor are commercially available and can readily be prepared. For example, U.S. Patent No. 5,530,101 describes antibodies that bind the IL-2 receptor, including the p75 component of the IL-2 receptor. An

adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). That which is conventional or well known to one of ordinary skill in the art need not be disclosed in detail (see also *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94). The MPEP § 2163 states:

> "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)."

Applicants submit that, given the guidance provided by the specification, the knowledge of one of skill in the art regarding antibodies that bind the IL-2 receptor, one of skill in the art could readily identify (or produce) antibodies of use. The antibodies include antibodies that bind p55 and antibodies that bind additional components of the IL-2 receptor (such as p75). Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly the metes and bounds of a symptom of any autoimmune disease cannot be determined. Applicants respectfully disagree with this assertion, and submit that a skilled clinician can readily identify the symptoms of an autoimmune disorder. However, solely to advance prosecution, claims 1-20 have been amended to be limited to methods for the treatment of multiple sclerosis. The symptoms of multiple sclerosis can be readily identified by a skilled clinician; specific parameters to be detected are set forth in the specification (for example, see pages 14-15). Applicants submit that the amendment of the claims renders the objection moot.

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly the metes and bounds of "a therapeutically effective combination" cannot be determined. Applicants respectfully disagree with this assertion, and submit that the metes and bounds of a

therapeutically effective combination of interferon beta and an antibody that binds the IL-2 receptor are clear and definite; the phrase refers to a therapeutically effective amount of both interferon beta and an antibody that binds the IL-2 receptor. However, solely to advance prosecution, the claims have been amended to recite "a therapeutically effective amount of interferon beta" and "a therapeutically effective amount of an antibody that specifically binds the interleukin-2 receptor," thereby rendering the rejection moot.

Rejections Under 35 U.S.C. § 102 (b)

Claim 20 is rejected as allegedly being anticipated under 35 U.S.C. § 102(b) over "Study of Zenapax." Applicants respectfully disagree with this assertion. However, solely to advance prosecution, claim 20 is amended herein to depend from claim 1. Applicants submit that the amendment of claim 20 (to depend from a claim not rejected as allegedly being anticipated by the prior art) renders the rejection moot.

Rejections Under 35 U.S.C. § 103

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as allegedly being anticipated over "Study of Zenapax" in view of Khoury et al., further in view of Paty et al. and further in view of. Jacobs et al. Applicants respectfully disagree with this rejection as applied to the claims as amended.

Study of Zenapax is a request for subjects to enroll in a clinical trial. The administration of a therapeutic regimen that includes the administration of Zenapax (also known as "daclizumab") is disclosed. Study of Zenapax does not describe the dose of Zenapax that will be administered, nor does Study of Zenapax describe the timing of administration of Zenapax.

Khoury et al. discloses that the presence of activated T lymphocytes correlates with the progression of multiple sclerosis. As noted in the Office action, Khoury et al. does not describe the effect of either interferon beta or Zenapax.

Paty et al. describes the administration of interferon-1 beta-1b to patients with multiple sclerosis. Paty et al. do not suggest, or render obvious, the use of any additional agents with interferon-1 beta-b for the treatment of multiple sclerosis, let alone the use of Zenapax.

Jacobs et al. teaches the administration of interferon-1 beta-1a to patients with multiple sclerosis. Jacobs et al. do not suggest, nor render obvious the use of any additional agents with interferon-1 beta-1a for the treatment of multiple sclerosis, let alone the use of Zenapax.

The Office action alleges that if two or more treatments are effective for the treatment of disease, it is obvious to combine these two treatments, and that the optimization of dosing is simply routine. Applicants respectfully disagree with these assertions.

Applicants submit that a combination of agents, each separately effective for the treatment of a specific disease, does not ensure a beneficial result when the agents are administered in combination. This is evidenced by Bowman et al. (Transplantation, 53: 556-9, 1992, abstract submitted herewith as Exhibit A). Treatment of renal transplant recipients with low-dose cyclosporine, azathioprine and prednisone (triple therapy) results in an increase in acute rejection episodes as compared to treatment with cyclosporine and prednisone (double-therapy). Triple therapy of renal transplant recipients also led to an increased infection rate as compared to double therapy. The addition of an agent (azathioprine) resulted in more acute rejection episodes, greater immunosuppression requirements, and a resultant increase in infections. Thus, the use of a combination of agents does not ensure a superior effect.

Agents that are of use individually for the treatment of a disease are often used at a different dose when used in a combinatorial therapeutic for the treatment of the same disease. For example, lower doses of tiazofurin and ribavirn can be used at significantly lower doses when they are used together for the treatment of experimental autoimmune encephalitis (an animal model of multiple sclerosis, see Exhibit B). In addition, a dose of a specific agent that is of use for the treatment of one disease may not be of use for treating another disease. For example, different doses of methotrexate are recommended for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and psoriasis (see Exhibit C).

The legal standard applicable to determinations of obviousness based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 472-3, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would suggest to one of ordinary skill in the art that this process shall be carried out and would have a reasonable expectation of success viewed in the light of the prior art. Both the suggestion and the expectation of success must be

found in the prior art, not in the applicant's disclosure [emphasis added, citation omitted].

Thus, (1) the prior art must suggest or provide an incentive for a combination of references, (2) the combination as suggested or motivated by the art must yield the process claimed, and (3) the prior art must provide an expectation of success. However, at no point may the applicants' disclosure be used to suggest, or provide incentive for, a combination of references.

Applicants submit that a disclosure relating to the treatment of multiple sclerosis using one type of therapy (such as interferon-beta 1b), does not necessarily suggest combination with another reference describing the treatment of multiple sclerosis using another type of therapy (such as interferon beta 1a). In addition, even if the impermissible combination were made, one of skill in the art must reasonably expect the claimed combination to work (see In re O'Farrell, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed Cir. 1988)). As evidenced by Exhibit A, a combination of multiple agents, each effective for the treatment of the same disease, may not provide a beneficial result. Moreover, as evidenced by Exhibit B, an agent that is of use individually for the treatment of one disorder at a specified dose may used in a combination therapy at an entirely different dose. Even if an agent is shown to be effective for multiple diseases, the agent can be used at entirely different concentrations and/or dosing schedules for different diseases, as evidenced by Exhibit C. Thus, even if one of skill in the art were to combine the teachings of Study of Zenapax, Khoury et al., Paty et al., and Jacobs et al. there is not a reasonable expectation that a dosing regimen wherein the antibody that specifically binds the interluekin-2 receptor is administered every other week for two weeks and then monthly, and/or wherein the wherein the antibody is administered at a dose of 1-2 mg/kg would be effective.

Reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

The Examiner is invited to telephone the undersigned if any questions remain concerning the amendments made herein. Otherwise, the present application is ready for substantive examination, and such action is requested.

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